MODELING the Molecular Basis of PARKINSON'S DISEASE

Using the IBM Blue Gene's considerable computer simulation power, researchers have made major strides in evaluating the molecular and environmental features that lead to the clinical diagnosis of Parkinson's disease and Lewy body dementia, as well as to strategies for pharmaceutical intervention and amelioration of Parkinson's disease. Their findings also have broad applicability to other diseases such as Alzheimer's disease, rheumatoid arthritis, type II diabetes mellitus, and spongiform encephelopathies (prion diseases).

As the second most common neurological disorder in adults, the personal, economic, and societal costs of Parkinson's disease are enormous. Every nine minutes, an individual is diagnosed with Parkinson's disease. Currently, there are more than 2 million cases in the United States, with 60,000 new cases diagnosed each year. In economic terms, the disease exacts an annual cost of $25 billion on the U.S. economy alone.

The devastating effects of Parkinson's disease are well known. The disease's progression is characterized by a decrease in limb mobility over time. The loss of movement is caused by the death of dopamine-producing cells in the brain. Familial studies suggest that disease progression is associated with defects that cause increased aggregation of a protein known as alpha-synuclein, or α-synuclein, which, in turn, leads to harmful ring-like or pore-like structures in human membranes, the kind of damage found in Parkinson's and Alzheimer's patients (figure 1).

"This important finding could lead to new therapies for Parkinson's disease by developing and modeling drugs."

Dr. Igor Tsigelny
UCSD

Molecular Basis of Disease

A study recently conducted by a research team from the San Diego Supercomputer Center (SDSC) at University of California–San Diego (UCSD) confirms what other researchers had suspected previously. "The present study—using molecular modeling and molecular dynamics simulations in combination with biochemical and ultrastructural analysis—shows that alpha-synuclein can lead to the formation of pore-like structures on membranes," states Dr. Igor Tsigelny, a project scientist in chemistry and biochemistry at UCSD and researcher at SDSC. "In contrast, beta-synuclein or β-synuclein appears to block the propagation of alpha-synucleins into harmful structures," he notes (figure 2, p54).

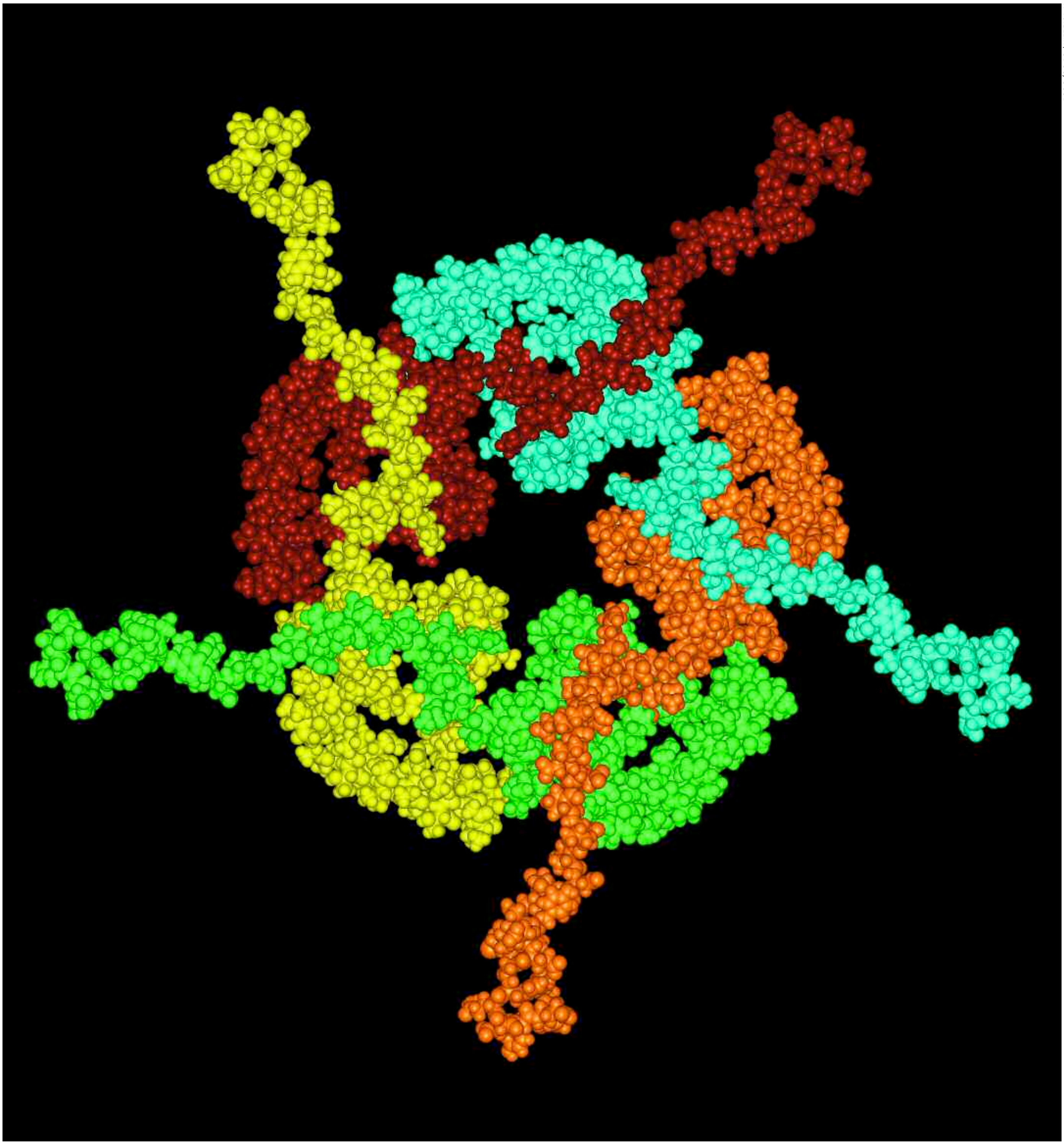

Figure 1. *Consecutive docking of a membrane-philic conformation of alpha-synuclein monomers on the membrane leads to the creation of a pentameric ring structure.*

The team's research represents a major step in evaluating the molecular and environmental features that lead to the clinical diagnosis of Parkinson's disease and Lewy body dementia, as well as strategies for pharmaceutical intervention and amelioration of the disease. "This important finding could lead to new therapies for Parkinson's disease by developing and modeling drugs that block alpha-synuclein aggregation and block and inhibit the abnormal calcium transport in the pores," explains Dr. Tsigelny.

Furthermore, this work has broad applicability to other diseases. The etiology of Parkinson's disease indicates that it is one in a family of at least 16 disorders characterized by the formation of amyloid plaques and inappropriate aggregation

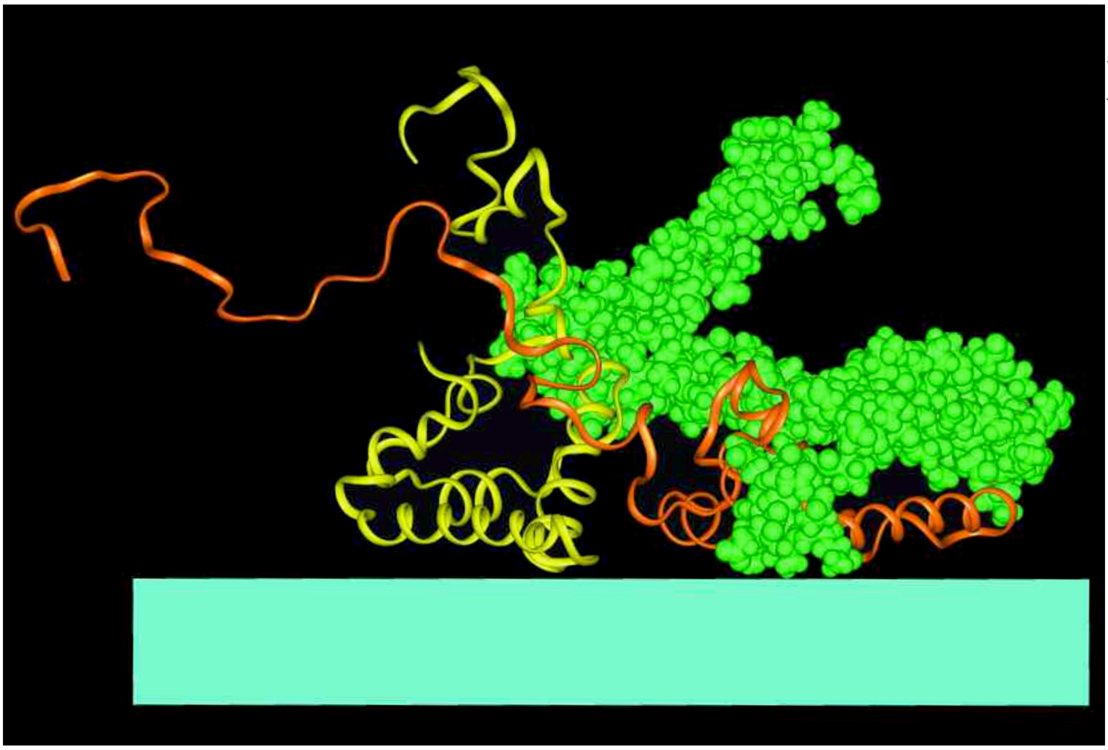

Figure 2. *Alpha-synuclein pentamer (yellow and orange ribbon diagram) construction interrupted by beta-synuclein (CPK).*

of proteins—key symptoms of disease progression. Among the related diseases are Alzheimer's disease, rheumatoid arthritis, type II diabetes mellitus, and spongiform encephelopathies (prion diseases). "Thus, the research effort being conducted will not only be informative in addressing the underlying molecular basis for Parkinson's disease, but will likely be instructive in identifying risk factors and therapeutic strategies for a large body of other diseases that are equally prevalent in human populations," explains Dr. Eliezer Masliah of the Departments of Pathology and Neurosciences at UCSD, and a member of the research team.

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Funding and Support

The research is being supported by funding from the National Institutes of Health (NIH), a U.S. Department of Energy Innovative and Novel Computational Impact on Theory and Experiment (INCITE) grant (sidebar "DOE INCITE Program Enables Breakthrough Science and Engineering"), and the SDSC/IBM Institute for Innovation in Biomedical Simulations and Visualization.

Through the INCITE program, the UCSD team received allocations of processor-hours in both 2006 and 2007 to conduct this research. These allocations enabled researchers to perform complex calculations for the study on high-performance Blue Gene/L computers at SDSC and the Argonne Leadership Computing Facility (ALCF; sidebar "The Argonne Leadership Computing Facility," p56). At the SDSC, researchers used a 6,144-processor, 13.8-teraflop IBM Blue Gene/L computer. At the ALCF, they used a 2,048-processor, 5.7-teraflop Blue Gene/L dedicated to a mix of INCITE projects and scalable software evaluation and development projects.

Computational and Experimental Approach

The team took a molecular-modeling/structural approach to uncover the maturation pathways of alpha-synuclein and beta-synuclein, focusing on protofibril structure development. The most recent evidence suggests that the protofibril intermediate structure of alpha-synuclein activates apoptosis in dopaminergic neurons. Other studies have noted that the protofibril structure can develop membrane pores with the capacity to promote transmembrane movement of calcium ions.

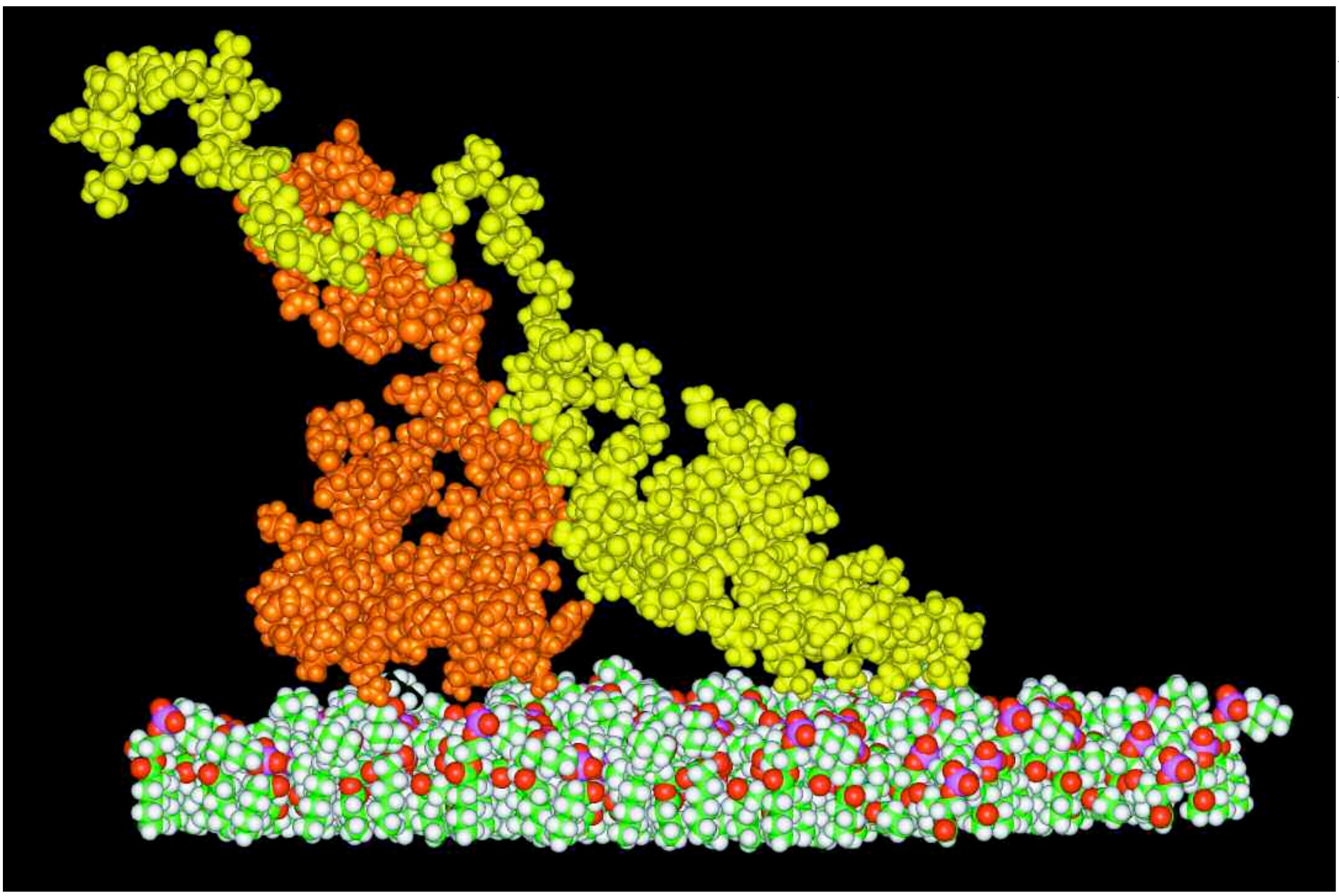
The researchers used high-end computing resources at ALCF and SDSC to generate hypotheses about the structural basis for the tendency of alpha-synuclein to aggregate and undergo pore formation and insertion into biological membranes (figure 3; figure 4, p56). The team is conducting this work in close association with ongoing biochemical and nuclear magnetic resonance (NMR) characterization of the alpha-synuclein protein, its variants, and its behavior in solution and micelles. In this way, they can quickly translate the results of modeling studies into a rapid iterative analysis that will test the pre-

DOE INCITE Program Enables Breakthrough Science and Engineering

To help research communities fully tap into the capabilities of current and future supercomputers, Department of Energy (DOE) Under Secretary for Science, Dr. Raymond Orbach, launched the Innovative and Novel Computational Impact on Theory and Experiment (INCITE) program in 2003. The INCITE program was conceived specifically to seek out computationally intensive, large-scale research projects with the potential to significantly advance key areas in science and engineering. Each year, the program continues to expand, with current research applications in chemistry, combustion, astrophysics, genetics, materials science, and turbulence.

In 2007, the Argonne Leadership Computing Facility (www.alcf.anl.gov) and IBM hosted nine INCITE projects that were allocated a total of 9.7 million CPU hours. The projects ranged from predicting protein structure to simulating the formation of foams. Through a partnership with IBM, these Blue Gene INCITE projects also had access to the 40,960-processor, 112-teraflop Blue Gene system at the IBM T.J. Watson Research Center in New York. Beyond providing access to powerful supercomputers, a key aspect of the INCITE program is to connect leaders of the projects with scientific and technical staff at the computing facilities. These staff, who are often scientists with a strong interest in computing, work closely with INCITE researchers to maximize the scientific output from the computer runs.

More details about the INCITE program are available on the DOE website (http://www.sc.doe.gov/ascr/incite/index.html). Each year, proposals from universities, other research institutions, and industry are encouraged (http://hpc.science.doe.gov/allocations/incite/).



I. Tsigelny, SDSC/UCSD

Figure 3. *Formation of the alpha-synuclein dimer on a membrane. Note that it is further aggregating toward the pore structure.*

dictions of their modeling work. Specifically, the researchers can correlate their predictions with direct measurements of aggregation, insertion of the proteins into membranes, and pore formation under specific conditions. These tests were conducted onsite using electrophysiological (patch-clamp) analysis and various biochemical techniques to quantitate the effect of conformational states of alpha- and beta-synucleins on the rate and extent of amyloid pore formation *in vitro*.

Highly parallel programs were explored as part of the multiprogram, multidata (MPMD) system needed to study large multimolecular biological systems. These include parallel versions of the

The Argonne Leadership Computing Facility

The Leadership Computing Facility Division operates the Argonne Leadership Computing Facility (ALCF) as part of the DOE effort to provide leadership-class computing resources to the scientific community. The mission of the ALCF, established in 2006, is to provide the computational science community with a leading computing capability dedicated to breakthrough science and engineering. The ALCF provides resources that make possible computationally intensive projects of the largest scale. ALCF staff members operate this facility for the DOE and also provide in-depth expertise and assistance in using ALCF systems and optimizing their applications.

DOE selects major ALCF projects through the INCITE program (sidebar "DOE INCITE Program Enables Breakthrough Science and Engineering," p55). This program seeks computationally intensive research projects of large scale that can make high-impact scientific advances through the use of a large allocation of computer time, resources, and data storage.

The ALCF installed a single rack Blue Gene/L system (BGL) in January 2005. The next-generation Blue Gene/P systems—to be called Endeavour and Surveyor—will be available in 2008. Endeavour will be an IBM Blue Gene/P system with 8,196 quad-core nodes and 16 terabytes of memory. Endeavour will be used primarily for production scientific and engineering computing, and 2008 INCITE proposals may request time on this system. Surveyor will be an IBM Blue Gene/P system with 1,024 quad-core nodes and two terabytes of memory, and it will be used primarily for tool and application porting, software testing and optimization, and systems software development.

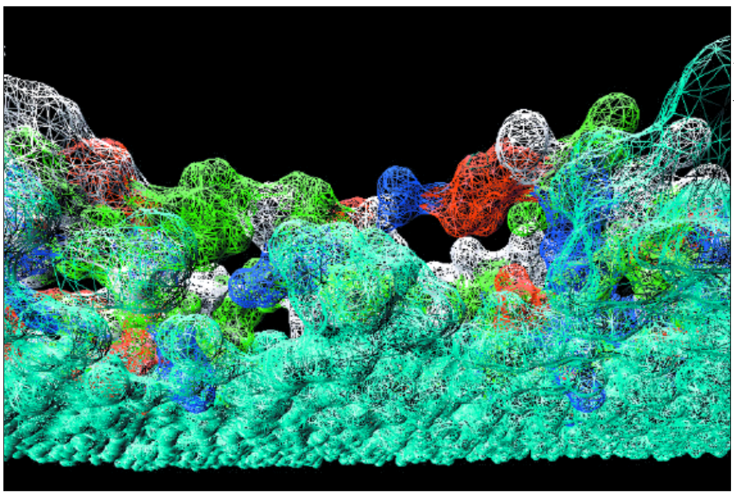


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Figure 4. *A membrane (cyan, cut from the bottom) embedded with the residues of alpha-synuclein pentamer (cut at the top on the level of the highest membrane atom).*

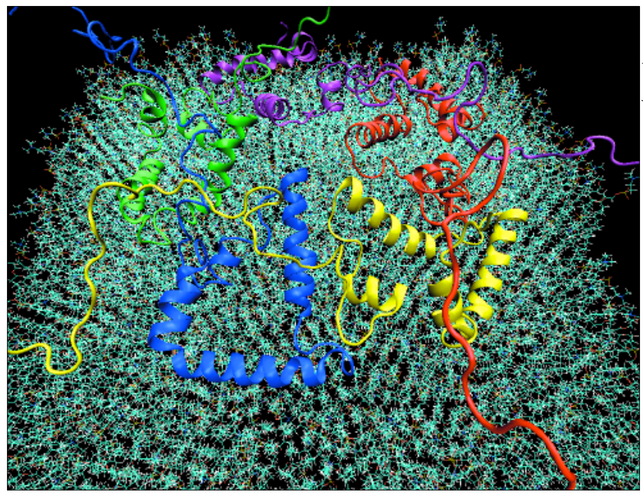

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Figure 5. *Alpha-synuclein pentamer constructed with 4ns molecular dynamics (MD) conformers after equilibration on the membrane with MD.*

Their work provides insights into the molecular mechanism for Parkinson's disease progression, as well as a test bed for identifying possible therapeutic interventions through computational modeling.

NAMD (NAnoscale Molecular Dynamics) package for molecular dynamics calculations and the DOT (Daughter of Turnip) package for molecular docking calculations, as well as the MAPAS program (Membrane-Associated Proteins Assessment) for calculation of membrane-association scores for proteins and protein aggregates. The programs enabled the team to make predictions for conformational changes of proteins, protein–protein interactions and/or aggregation, and interaction of proteins individually or as a complex with the membrane. Each of these events was simulated with a separate program.

Notably, the computational work being conducted has significant benefits in driving the creation of new simulation capabilities. The work requires the researchers to adapt existing tools for molecular simulation to the new Blue Gene architecture. The architecture is unique in providing a very dense processor array but at the cost of a relatively small amount of memory per computational node. As a result, the strategies for running simulations on this platform require the adaptation of existing community codes to a new computing paradigm. For example, the utility of the community code CHARMM is restricted on the Blue Gene, because it requires the full list of data objects to be resident at each node. Currently, efforts are under way at SDSC, IBM, and elsewhere to adapt the existing codes to this new platform.

Science Accomplishments

In the fiscal year 2006, using the allocation provided by the INCITE grant, researchers completed a comprehensive molecular dynamics study of the interaction of alpha-synuclein with model membranes. The study examined the initial stages

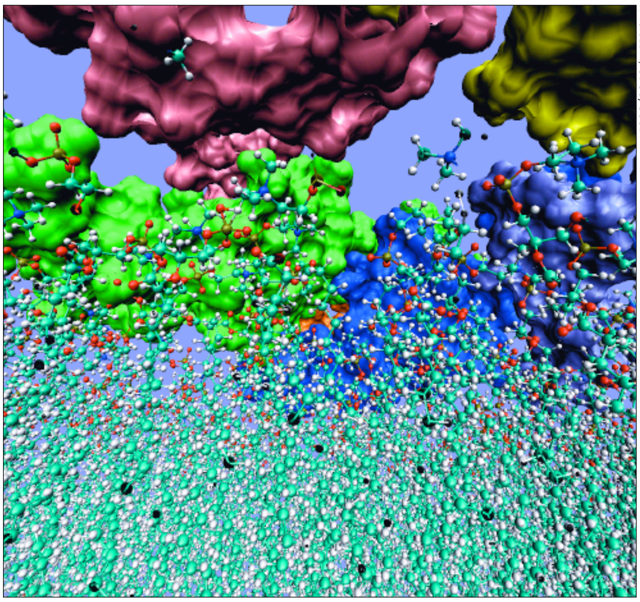

Figure 6. *Alpha-synuclein pentamer constructed with 4ns MD conformers (solid surfaces) after equilibration on the membrane (ball-and-stick) with MD.*

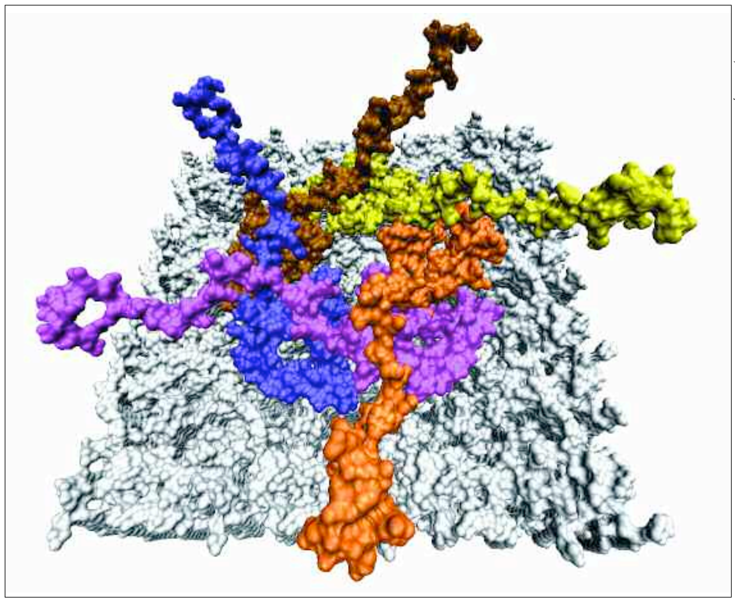

Figure 7. *Pentamer of alpha-synuclein 4ns MD conformers on the membrane.*

of formation of pore-like oligomeric alpha-synuclein structures on the membrane (figures 5, 6, and 7). Furthermore, they conducted molecular dynamics studies of the impact of beta-synuclein on pore-like oligomer formation. The results predicted that beta-synuclein would prevent formation of the pore-like structures at the surface of the membrane. Both the predicted pore-like structure by alpha-synuclein and the interference of beta-synuclein with pore formation are consistent with experimental results obtained in the partners' laboratories at UCSD. The researchers also used the resources to create and test a method for elucidation of membrane-contacting proteins.

Their work provides insights into the molecular mechanism for Parkinson's disease progression, as well as a test bed for identifying possible therapeutic interventions through computational modeling. These insights will help focus the search for treatment, based on an improved understanding of the molecular mechanisms of the disease's progression. The test bed offers a computational framework for generating hypotheses about treatments that can be adapted readily to state-of-the-art, high-throughput virtual screening of pharmacophores as potential lead compounds. Academic and pharmaceutical companies could use such a modeling system for further testing and improving potential pharmacophores and other palliative therapies.

Ongoing Research

In work currently under way, the researchers are conducting a more comprehensive investigation of alpha-synuclein penetration into the membrane, including a thorough study of pore creation. They are employing a computational approach similar to that used earlier—the NAMD molecular dynamics package, along with the MAPAS program and a set of docking programs on the Blue Gene/L computer system.

The scope of the team's work has increased in both the number of simulations being conducted and in the scale of the simulations. The simulations are focusing on the interaction of higher-level alpha-synuclein oligomers with the membrane, which increases the number of atoms in the system up to approximately 800,000. Given the encouraging correlation between the molecular dynamics modeling predictions and laboratory experimental results, the team expects to make steady progress with the computational model for Parkinson's disease progression and design of effective drugs based on computational modeling and simulations. ●

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Contributors: Dr. Igor Tsigelny of UCSD and SDSC worked in collaboration with the following UCSD colleagues: Dr. Pazit Bar-On, Neurosciences; Dr. Yuriy Sharikov, SDSC; Dr. Leslie Crews, Pathology; Dr. Makoto Hashimoto, Neurosciences; Dr. Mark A. Miller, SDSC; Dr. Steve H. Keller, Medicine; Dr. Oleksandr Platoshyn, Medicine; Dr. Jason X. J. Yuan, Medicine; and Dr. Eliezer Masliah, Pathology and Neurosciences.

Further Reading

I. F. Tsigelny et al. 2007. Dynamics of α-synuclein aggregation and inhibition of pore-like oligomer development by β-synuclein. *FEBS J.*, **274 (7):** 1862–1877.